52. (new) An isolated mutant according to claim 50, wherein the *Hepadnavirus* is woodchuck hepatitis virus.

53. (new) An isolated mutant according to claim 50, wherein the *Hepadnavirus* is duck hepatitis virus.

54. (new) A method for screening the antiviral potential of anti-HBV agents against HBV mutants which have decreased sensitivity to a nucleoside analogue relative to an isolated wild type HBV, said method comprising measuring the lethal dose of said agents against said mutants or against related *Hepadnaviruses* bearing the same mutation.--

REMARKS

Reconsideration is requested.

Claims 1-31 have been canceled, without prejudice.

Claims 32-54 have been added and are pending. No new matter has been added.

Attached is a certified copy of the priority document. Acknowledgement of the same is requested and, at a minimum, withdrawal of the Section 102 rejection of claims 1, 4-9, 13 and 17 over Bartholomew (Lancet 349:20-22, January, 1997) is requested.

The Examiner has not found the applicants' traversal of the restriction requirement to be persuasive, however the Examiner continues to assert that the "searches are not co-extensive, and therefore impose additional burden." See, page 2 of the Office Action dated April 9, 2001 (Paper No. 17). The Examiner has not provided

an indication of what further subject matter would need to be searched. Specifically, the Examiner has admitted that the subject matter of Groups I, II and III were classified in Class 435, sub-class 325.1. Moreover, the Examiner's Groups IV and V are classified, by the Examiner, in Class 435, sub-class 5. The classification index, according to the applicants' understanding, is used to define separate areas of search and separate subject matter which has been found, by the Patent Office definition, to define separate areas of search. The Examiner has not indicated in Paper No. 17 what further areas of the classification index are required to be searched, for example, which would require an undue burden on the Examiner. While the applicants appreciate the Examiner's inclusion of claims 9, 11 and 18 into the search of the elected Group I, the applicants again request reconsideration and withdrawal of the restriction requirement.

The applicants appreciate the Examiner's acknowledgement of the possibility of rejoinder and have maintained many of the method claims for further possible rejoinder.

Finally, the Examiner indicates, within the context of a Section 112, second paragraph, rejection that the Examiner would be

> "willing to consider examining some claims directed to methods of analysis, particularly if the claims focus upon detection of applicant's specific disclosed mutations in human hepatitis B virus (and are not broadly directed to detecting any mutation in polymerase domain B or C or any mutation altering the overlapping region AA118-207 of the S antigen, for any para-retrovirus or any non-human hepatitis B virus)." See, page 6 of Paper No. 17.

While the Examiner's willingness to examine method claims of the specified scope is acknowledged, with appreciation, the comment is not understood in the context of Section 112, second paragraph rejection stated on pages 4-6 of Paper No. 17.

Moreover, the Examiner's comment with regard to the apparent exclusion of non-human hepatitis B virus is not understood, and clarification is requested, as the Examiner has rejected a number of the claims over Fischer et al (Anti-Microbial Agents and Chemotherapy, Vol. 40, No. 8, August, 1996, pages 1957-1960), which discloses generation of duck hepatitis B virus polymerase mutants through site directed mutagenesis. Accordingly, it would appear that the Examiner has not limited her search of the art to human hepatitis B virus or believes the non-human virus is indefinite.

The Section 112, second paragraph, rejection of claims 1, 4-9, 11, 13, 16-18 and 23-31 is moot in view of the above. The applicants respectfully submit that the pending claims are definite and the Examiner's consideration of the following in this regard is requested.

The Examiner has objected to the use of the term "variant" as being a relative term. While not agreeing with the Examiner, the applicants have recited "mutant" in the pending claims. The applicants believe either term is well recognized and the metes and bounds of either term will be recognized by one of ordinary skill in this art. The applicants have also specified that the reduced sensitivity recited in the claims is relative to wild type virus. Moreover, the applicants note that comparison of the wild type and mutant polymerase sequence is not essential for such a comparison. That is, one of ordinary skill in the art will appreciate that a mutant virus may be recognized by a functional effect, such as has been noted by the Examiner on page 3 of Paper No. 17. The phrase objected to in claims 7, 8, 26 and 27 has not been repeated such that the Examiner's objection regarding the same is moot in view of the above.

Moreover, the objections to the style in which claim 17 had been written is moot in view of the above. The objected-to phrase "a variant of an isolated DNA virus" and the Examiner's objection to the same are moot in view of the above. Specifically, the presently claimed invention is not directed to a product of nature. Even if the claims did read on a product of nature, such a concern is not appropriately addressed within the context of Section 112, second paragraph, but rather under Section 101. More importantly, the specification certainly teaches how to make the claimed invention from either a patient sample or *de novo*. The Examiner's citation of Fischer et al (citation above) clearly indicates that site directed mutagenesis was a tool available to one of ordinary skill in the art to make mutants and variants. As noted by the Examiner, such mutants and variants are useful "for purposes of diagnosis and/or a choice of treatment regimens", for example. See, page 5 of Paper No. 17. Moreover, infectious clones of HBV were used, such as are described by the attached article by Sells et al (DNAS 84 (4): 1005-9 (1987)). Certainly, the level of ordinary skill in the art was advanced in this regard as of the time of the present invention.

Finally, the applicants note the Examiner's concern with regard to one of ordinary skill being able to make the claimed invention, within the context of Section 112, second paragraph, as stated on page 6 of Paper No. 17, appears to be more appropriately addressed under Section 112, first paragraph. In any event, the applicants submit that one of ordinary skill in the art would have been able to make the presently claimed invention from a review of the specification as well as the generally advanced level of skill in the art at the time of the present invention.

The Examiner states in comment "(4)" that it is "not clear how one would *use* all the claimed variant viruses." See, page 6 of Paper No. 17. Again, this concern appears to be more adequately addressed under Section 112, first paragraph, as opposed to the Section 112, second paragraph, rejection. In any event, the applicants submit that engineered viruses will be useful in a manner similar to those obtained from patients. One of ordinary skill in the art will appreciate that mutants identified in humans, ducks or, for example, woodchucks can be made or engineered to bear this mutation. These mutations can serve, for example, to test for resistance *in vitro*, testing for cross-resistance and drug screening, by means known by those of ordinary skill in the art.

The Section 101 rejection of claims 1, 4-9, 11, 13, 16, 17, 18 and 23-31 is moot in view of the above. The present claims define patentable subject matter. While the claims have been amended to recite "mutant" the applicants note the Examiner appears to recognize that isolated variants are patentable subject matter.

The Section 112, first paragraph, rejection of claims 9, 11, 13, 16-18 and 28-30 is moot in view of the above. The claims are submitted to be supported by a written description which, the applicants believe, one of ordinary skill in the art would believe is sufficient to demonstrate the applicants were in possession of the claimed invention at the time the application was filed. The Examiner is requested to consider the following in this regard.

The Examiner is requested to appreciate that the mutations of the invention will mainly occur in, or around, the B and/or C domain of the DNA polymerase. The B domain spans approximately 20 amino acids while the C domain spans approximately

ten amino acids. Nucleic acid mutations which lead to the mutated DNA polymerase, and testing for the effect of the same, especially with regard to drug sensitivity, would not have required undue experimentation, after one of ordinary skill in the art reviewed the present specification. The Examiner will also appreciate that the amino acid positions within the DNA polymerase are specified and their consensus sequence is provided, for example, at page 6 of the specification. Proximal regions are defined as well, for example, on page 6 of the specification. Finally, testing for drug sensitivity, for example, would not have required undue experimentation as illustrated in exemplified assays provided in the specification.

As for the Examiner's concern over overlapping regions, the applicants note that the mutants of the polymerase sequence and reduced immunoreactivity of S antigen generally occur when a mutation occurs in the B and/or C domain of the DNA polymerase and in the part of the surface antigen that overlaps with the regions of the DNA polymerase. As noted above, the B and/or C domains of the DNA polymerase are small and generally known to one of ordinary skill in the art. Finally, the applicants submit that antibodies to the surface antigen were available in the art, a person of ordinary skill could have easily tested a reduced interactivity with immunological components, in addition to a decreased sensitivity to nucleoside analogues.

As for the Examiner's criticism of claims 17 and 18, the applicants note that the claims have been rewritten as, for example, claims 42 and 43 and have been made dependent on independent claim 40. The revised claims also positively state that SEQ ID NO:17 and related sequences must contain the noted substitution in the DNA

polymerase and the substitutions in the surface antigen. The applicants submit the claimed invention is sufficiently described in the application such that one of ordinary skill would appreciate the applicants were in possession of the claimed invention at the time the application was filed.

The Section 112, first paragraph, rejection of claims 1, 4-9, 11, 13, 16, 17, 18, and 23-31 is moot in view of the above. The claimed invention is submitted to be supported by an enabling disclosure and the Examiner is requested to consider the following in this regard.

Initially, the applicants note that, while not being required by the statute, rules, or MPEP, the application does teach a working example of the viruses *per se*. The Examiner is requested to see, for example, Example 4 of the specification in this regard. Moreover, methods to create mutant viruses *in vitro* were well known in the art at the time of the present invention. See, for example, Fischer et al, cited by the Examiner. The applicants note the claims are now directed, in part, to *Hepadnaviruses* to advance prosecution. There is a clear relation between HBV and the animal models, as appears to be acknowledged by the Examiner's reliance on Fischer et al. Further, the specification describes, for example, the relatedness of the DNA polymerases at page 2, lines 13-18, Figure 3 and page 3, line 24. The use of such *in vitro* models for HBV is well known in the art. As noted above, Example 4 of the specification teaches an example of how one of ordinary skill in the art could screen the effect of an antiviral agent on the virus. The same type of assay can be used to screen for agents that can mask the effects of the mutation.

The claims are submitted to be supported by an enabling disclosure.

The Section 102 rejection of claim 1 over Chenault et al (Biochimie 76:3-8, 1994) is moot in view of the above. The pending claims, which are directed to *Hepadnaviruses* and, specifically, HBV, are patentable over the cited reference which relates to Caulimoviruses, which belong to the class of plant pararetroviruses. Accordingly, the claims submitted to be patentable over the cited reference.

The Section 102 of claims 1, 4-8, 17, 23-26 and 29 over Norder et al (Virology 198:489-503, 1994) is moot in view of the above. The pending claims are submitted to be patentable over Norder as the publication relates to two new HBV genotypes, genotypes E and F, which include silent mutations in the polymerase protein due to genotypic differences within HBV. The presently claimed invention does not include silent mutations in the polymerase protein, i.e., mutations which do not alter the HBV phenotype or protein sequence. The claims are submitted to be patentable therefore over Norder.

The Section 102 rejection of claims 1, 4-8, 11 and 23-27 over Fischer is moot in view of the above. The pending claims are submitted to be patentable over Fischer and consideration of the following in this regard is requested.

Fischer relates to duck hepatitis virus mutants that were artificially created to contain an amino acid change in a region analogous to the YMDD motif of the HIV reverse transcriptase. More specifically, the M512V and MI512VM mutants are disclosed. The resistance of these mutants to lamivudine is discussed.

Fischer admits however that

> "Resistance to lamivudine has not been seen in ducks chronically treated for one year, or in human studies using lamivudine to treat chronic hepatitis B infection [see, page 1957, left column, second paragraph].... To date, the development of resistance to antihepadnavirus agents has not been demonstrated either *in vitro* or *in vivo*. ... This report of a genetically engineered lamivudine-resistance hepadnavirus serves as a cautionary note of what could occur when lamivudine is used in a prolonged treatment of chronic HBV infections, analogous to the emergence of 3TC resistance in the treatment of AIDS." (see, page 1959, left column, first full paragraph, (citations omitted).)

There was, therefore, no evidence in Fischer of lamivudine-resistant HBV. Fischer teaches duck hepatitis virus mutants. Accordingly, Fischer fails to anticipate the claimed invention. As for the duck hepatitis mutants described by Fischer, the mutants were artificially produced, *in vitro*, and there is no evidence in Fischer of lamivudine treated ducks or humans producing such mutants. Moreover, Fischer does not specifically or inherently provide evidence that a M550V mutation in HBV would be resistant to lamivudine or other nucleoside analogues.

The pending claims are not anticipated by Fischer. The claims are submitted to be patentable over Fischer.

The Section 102 rejection of claims 1, 4-6, 9, 11, 17, 23-25 and 28-31 over Tipples et al (Hepatology 24(3): 714-717, September, 1996) is moot in view of the above. The pending claims are submitted to be patentable over Tipples, which discloses a lamivudine-induced change in the HBV polymerase from YMDD to YIDD in the C domain. Tipples does not disclose, for example, famciclovir and/or penciclovir-induced mutations or mutations in the DNA polymerase consisting essentially of the B

domain, as presently claimed. Moreover, Tipples fails to teach, literally or inherently, mutants exhibiting reduced sensitivity to penciclovir and/or famciclovir.

The claims are submitted to be patentable over Tipples.

The Section 102 rejection of claims 1, 4-9, 11, 13, 16-18 and 23-31 over Ling (Hepatology 24(3): 711-713, September, 1996) is moot in view of the above. The pending claims are submitted to be patentable over Ling and consideration of the following in this regard is requested.

Ling discloses lamivudine-induced mutant HBV sequences from two patients. The disclosed mutations are in the B and C domain of the HBV polymerase. Ling does not disclose, for example, famciclovir or penciclovir mutants. More importantly, Ling teaches that:

> "[t]he significance of [L526M and F512L] mutation[s] is unclear."See, page 712, left column, first full paragraph and page 713, left column, line 8.

Accordingly, Tipples fails to teach an HBV mutant or methods of using the same, as presently claimed.

The claims are submitted to be patentable over Ling.

In view of the above and attached, the claims are submitted to be in condition for allowance and a Notice to that effect is requested.

Respectfully submitted,

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By: _____

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